tissue an effective amount of a tyrosine kinase inhibitor in combination with a therapy that is effective to induce apoptosis or to increase the rate of apoptosis in the cell or tissue.

2. The method of claim 1, wherein the mutant EGFR gene is constitutively active.

3. The method of claim 2, wherein the mutant EGFR gene is ΔEGFR.

4. The method of any of claims 1 to 3, wherein the cell or tissue is a tumor selected from the group consisting of glioma, breast cancer, lung cancer and ovarian cancer.

5. The method of claim 4, wherein the tumor is a glioma.

6. The method of claim 1, wherein the apoptosis inducing or apoptosis rate increasing therapy is the administration of an agent selected from the group consisting of cisplatin, paclitaxel and vincristine.

7. The method of claim 1, wherein the tyrosine kinase inhibitor is relatively selective for a tumor specific mutant EGFR.

8. The method of claim 1, wherein the tyrosine kinase inhibitor is selected from the group consisting of Tyrphostin AG1478 and its derivatives.

9. A pharmaceutical composition comprising:

(A) an amount of an agent that is effective to induce apoptosis or increase the rate of apoptosis in a target cell or tissue; and

(B) an amount of a tyrosine kinase inhibitor that is effective to reduce the resistance to the induction of apoptosis or resistance to the

increased rate of apoptosis in the target cell or tissue, the resistance being mediated by a mutant EGFR.

10. The composition of claim 9, wherein the apoptosis inducing or apoptosis rate increasing agent is an antitumor agent selected from the group consisting of cisplatin, paclitaxel and vincristine.

11. The composition of claim 9, wherein the tyrosine kinase inhibitor is relatively selective for a tumor specific EGFR.

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12. The composition of claim 9, wherein the tyrosine kinase inhibitor is selected from the group consisting of Tyrphostin AG1478 and its derivatives.

13. A kit for treating cancer comprising

(A) an amount of an agent that is effective to induce apoptosis or increase the rate of apoptosis in a target cell or tissue; and

(B) an amount of a tyrosine kinase inhibitor that is effective to reduce the resistance to the induction of apoptosis or resistance to the increased rate of apoptosis in the target cell or tissue, the resistance being mediated by a mutant EGFR.

14. The kit of claim 13, wherein the apoptosis inducing or apoptosis rate increasing agent is an antitumor agent selected from the group consisting of cisplatin, paclitaxel and vincristine.

15. The kit of claim 13, wherein the tyrosine kinase inhibitor is relatively selective for a tumor specific EGFR.

16. The kit of claim 13, wherein the tyrosine kinase inhibitor is selected from the group consisting of Tyrphostin AG1478 and its derivatives.

I. STATUS OF THE CLAIMS

Claims 1-16 are pending in this case and have been examined.

Claims 1-16 were rejected under 35 USC § 112, second paragraph.

Claims 1-16 were rejected under 35 USC § 103.

II. REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The Office Action rejected claims 1-16 under USC 35 § 112, second paragraph, asserting that various claim terms are vague and indefinite.

On pages 2 and 3 of the Office Action, the terms "the apoptosis inhibiting effect" and "the step" in claim 1 and the terms "the resistance", "the induction" and "the increased rate" in claims 9 and 13 were found to lack antecedent basis. In the sole interest of furthering prosecution, claim 1 has been amended to refer to "an apoptosis inhibiting effect" and to delete the phrase "the step of." Concerning claims 9 and 13, Applicants note that MPEP § 2173.05(e) indicates that claims should be rejected only when there is uncertainty as to which limitations are being referred to with the use of the word "the." No rejection, however, should be made when the scope of the claim is reasonable ascertainable by those skilled in the art. Respectfully, that is the case here where it is clear that none of the cited phrases are referring back to another element or limitation. Respectfully, withdrawal of the rejection of claims 9 and 13 would be appropriate.

On page 3 of the Office Action, the term "relatively selective" in claims 7, 11 and 15 was found to be indefinite because "it is not adequately defined in the specification." Respectfully, this term is defined in the application on page 12 wherein the inhibitors relatively selective for tumor specific *EGFR* mutations "will reduce or avoid any deleterious side effects that may result from the use of agents that also modulate the activity of wild type EGFRs." Further, on page 13 of the application, an agent is considered to be relatively specific for a mutant EGFR when it has

"a relatively greater affinity for such a mutant than for a wild type EGFR. Preferred agents will be substantially more specific for mutant forms of EGFR and will be relatively specific for mutant forms of EGFR that are substantially tumor specific." Applicants respectfully request that this rejection be withdrawn.

On page 3 of the Office Action, the term "derivatives" in claims 8, 12 and 16 was found to be indefinite. Respectfully, the term "derivatives" is fully defined on page 26 as being "those having decreased toxicity, greater selectivity, [and] greater bioavailability." Accordingly, the specification fully describes the scope and meaning of the term "derivative" and withdrawal of this rejection would be appropriate.

On page 3, claims 9 and 13 stand rejected because they do not refer to a mutant EGFR gene. Applicants appreciate the suggestions to recite this phrase in the claims but respectfully note that both claims expressly recite that the resistance is "mediated by a mutant EGFR."

III. REJECTION UNDER 35 U.S.C. § 103(a)

The Office Action rejected claims 1-16 under §103(a) as being unpatentable over Han *et al.* in view of the Reed U.S. patent (5,831,066).

The Office Action essentially asserts that it would have been obvious to combine a tyrosine kinase inhibitor (such as Tyrophostin AG1478) in combination with a therapy that is effective to induce apoptosis or to increase the rate of apoptosis in the cell or tissue (such as cisplatin, paclitaxel or vincristine) "to obtain the expected combination of therapeutic benefits with regard to cancer treatment" (page 6, lines 16-17 of the Office Action). The Office action then asserts that "an ordinary skilled worker would have expected the claimed combination therapy to result in modulation of the apoptosis-inhibiting effect of ΔEGFR" (page 7, lines 1 and 2 of the Office Action).

Applicants respectfully submit that the Office Action fails to provide the requisite motivation from the prior art to combine the claimed classes of compounds. In order to establish

a *prima facie* case of obviousness, the prior art itself must: (1) suggest to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) reveal that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q. 2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 U.S.P.Q. 2d 1941 (Fed. Cir. 1992); *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q. 2d 1529, 1531 (Fed. Cir. 1989). In the absence of any teaching or suggestion in the references cited by the Office Action to practice the claimed methods, a *prima facie* of obviousness has not been set forth.

Applicant's invention is predicated on the discovery that the expression of mutant EGFR genes in cancer cells can suppress the apoptosis inducing activity of chemotherapeutic agents (see page 8 of the specification). Without such a discovery, Applicants respectfully submit that there would be no motivation to combine the claimed classes of agents. The motivation provided in the rejection at page 6, lines 16-17, where it is stated that the requisite motivation was "to obtain the expected combination of therapeutic benefits with regard to cancer treatment", respectfully is not found in the cited references. For instance, neither reference suggests that a tyrosine kinase inhibitor such as Tyrophostin AG1478 should be used in combination with the claimed class of apoptosis inducing drugs. Respectfully, the Han *et al.* reference does not even mention the word "apoptosis."

To remedy these lack of teachings in the cited references, it appears that the Office Action is relying in the teachings of the specification. For instance, at page 7, lines 1 and 2, the Office Action asserts that "an ordinary skilled worker would have expected the claimed combination therapy to result in modulation of the apoptosis-inhibiting effect of ΔEGFR." Respectfully, neither reference discloses that ΔEGFR is even involved in the modulation of the apoptosis in a tumor cell. As discussed above, this discovery can be found only in the instant application. Respectfully, reliance on this motivation to combine the references is improper.

It also appears that the Office Action indicates in the paragraph spanning pages 8 and 9, that combinations of known ingredients are *per se* unpatentable if they are combined for their

known characteristics. Respectfully, there is no such *per se* rule. Rather, a combination may be patentable whether it be composed of elements all new, partly new or all old. *Rosemont, Inc. v. Beckman Instruments, Inc.*, 221 USPQ 1 (Fed. Cir. 1984). Furthermore, even with a combination of "old elements" the prior art must suggest the combination to one of ordinary skill in the art. *Fromson v. Advance Offset Plate, Inc.*, 225 USPQ 26 (Fed. Cir. 1985). As discussed above, neither of the cited references provides the requisite suggestion to combine the claimed agents.

Lastly, even if, *ad arguendo*, it might have been of interest to attempt the claimed methods, "obvious to try" is not the standard for asserting or maintaining a *prima facie* rejection for obviousness. See, *e.g.*, MPEP §706.02(j); and *Ex parte Goldgaber*, 1995 Pat. App. LEXIS 7 (Bd. App. Int. 1995).

In view of the foregoing discussion, Applicants respectfully submit that the Office Action has not adduced a legally sufficient *prima facie* case of obviousness. Accordingly, reversal of the rejection would be appropriate.

IV. DUPLICATE CLAIMS

The Office Action on page 2 indicates that the kits of claims 13-16 are substantial duplicates of the compositions of claims 9-12 because the claimed kits do not contain added components. Respectfully, the kits of claims 13-16 recite the term "comprising". Accordingly, the claimed kits may include other components. Furthermore, the compositions of claims 9-12 contain the two recited classes of agents in a single formulation. The kits of claims 13-16 do not require that the claimed classes of compounds be provided in a single formulation. For these reasons, the kits of claims 13-16 are substantially different than the compositions of claims 9-12 and certainly not substantially duplicative under section 706.03 of the MPEP.

CONCLUSION